UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,593	07/21/2000	Nanda de Groot	4497US	4769

7590 12/31/2002

Allen C. Turner
Trask, Britt
P. O. Box 2550
Salt Lake City, UT 84110

EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 12/31/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/621,593	Applicant(s) DE GROOT ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 26-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 26-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 October 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *20* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Non-Final Rejection

Claims 1 and 26-36 are pending examination.

Applicants' traversal, amendment to the abstract, amendment to claims 27 and 34 in paper no. 22 is acknowledged and considered.

Specification

The amended abstract because of the word "means" is acknowledged, however, applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "**means**" and "**said**," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The abstract of the disclosure is objected to because of the word "said". Correction is required. See MPEP § 608.01(b).

Claim Objections

Claim 29 is objected to because of the following informalities: grammatical error improper term "farm-animal." Amending the claim to recite "farm animal," would obviate this objection.

Claim 1 is objected to because it reads on a non-elected invention. Applicants elected non-human transgenic animals in paper no. 10. However, the claim reads on the non-elected invention comprising delivering *in vivo* a nucleic acid encoding a pIgR protein to any animal

including any transgenic animal because the step for producing a transgenic non-human animal is missing from the body of the claim.

The rejection for claims 26-27, 32 and 34 under 112 new matter is moot in view of the applicants' traversal and the amendment to claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 26-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) A transgenic farm mammal, whose genome comprises a stably integrated recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein, wherein said mammal over-expresses said pIgR protein in its mammary gland compared to the expression of the pIgR protein in a mammary gland of a wild-type farm mammal, and wherein said protein is capable of transporting a first immunoglobulin protein across the basolateral side of a mammary epithelial cell to the epithelial cell's apical side, wherein the first immunoglobulin is selected from the group consisting of IgM and IgA and the second protein is IgG; 2) A method of making the transgenic farm mammal of 1, said method comprising: producing a DNA construct comprising a nucleic acid encoding pIgR protein operably linked to a promoter capable of driving expression of said pIgR protein in a mammary epithelial cell; introducing said DNA construct into fertilized eggs; and implanting the fertilized

eggs into a pseudopregnant female farm mammal, thereby product the transgenic farm mammal of 1), whereby the concentration of IgM or IgA is increased on the mammary gland cell's apical side compared to IgG on the mammary gland's basolateral side; 3) A method of collecting an immunoglobulin protein selected from IgM or IgA from the transgenic farm mammal of 2), comprising: providing the transgenic farm mammal of 2; and collecting milk comprising said immunoglobulin protein from the mammary gland of said transgenic farm mammal; and does not reasonably provide enablement for the entire scope of the claimed embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The claimed invention is directed to the making and using a transgenic animal whose genome comprises a stably integrated recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein, wherein said animal over-expresses said pIgR protein compared to the expression of the pIgR protein in a wild-type animal. The invention lies in the field of producing transgenic non-human animals.

The state of art teaches how to make and use transgenic mammals whose genome expresses a heterologous gene product (US Patent No. 5,895,833).

The specification displays transgenic mice whose genome comprises a recombinant nucleic acid encoding a murine pIgR capable of transporting an immunoglobulin from a mammary epithelial cell's basolateral side to the cell's apical side (pages 2 and 3). The

specification further provides teachings that pIgR is capable of transporting dimeric IgA across the epithelial cells of mucosal surfaces into the external secretions and raising the concentration of IgA relative to IgG in external secretion (pages 6 and 7).

In view of the In Re Wands Factors, the specification only provides sufficient guidance or evidence for one skilled in the art to make and use a transgenic farm mammal whose genome comprises a stably integrated recombinant nucleic acid encoding a polymeric immunoglobulin receptor (pIgR) protein. The claims read on a transgenic farm animal whose genome comprises a recombinant nucleic acid encoding pIgR protein, wherein the protein has a function limitation and does not recite a phenotype.

[Note that although the claimed transgenic non-human farm animal is not limited to expression of the protein at a level resulting in a specific phenotype, with regard to the claims breadth, the standard under 35 U.S.C. 112, first paragraph, entails the determination of what claims recite and what the claims mean as a whole. In addition, when analyzing the enabled scope of the claims, the teachings of the specification are to be taken into account because the claims are to be given their broadest reasonable interpretation that is consistent with the specification. As such, the broadest interpretation of the claimed transgenic non-human farm animal having cells, which harbor a recombinant nucleic acid that expresses the protein at a level sufficient to result in a specific phenotype (i.e., it is unknown what other purpose the transgenic animal would serve if the transgene is not expressed at a sufficient level for a resulting phenotype).]

Thus, the claims do not describe a phenotype (e.g. over-expresses pIgR at least 10 fold higher than the expression of the pIgR in a wild-type farm animal) and are not considered enabled.

Furthermore, with respect to claim 1, which encompasses delivering a nucleic acid encoding pIgR to a non-human farm animal, including transgenic non-human farm animal, the claimed method is not considered enabled for the full scope of the claimed method. The breadth of the term "non-human farm animal" reads on any non-human farm animal and the body on the claim reads on delivering a nucleic acid to any non-human farm animal. However, the elected invention is directed to producing transgenic non-human farm animals whose epithelial cells of the mammary gland comprise a nucleic acid encoding a pIgR protein. The claim is missing a step of producing and providing said transgenic non-human farm animal to complete the pre-amble of the claim. The specification only provides guidance for one skilled in the art to make a transgenic non-human mammal whose mammary gland over-expresses pIgR. The claim further encompasses raising the concentration of a first class of immunoglobulin relative to a second class of immunoglobulin in any compartment of a body (including mammary gland) of a transgenic non-human farm animal comprising administering a nucleic acid to a mammary gland of a non-human farm animal. The specification only provides sufficient guidance for raising the concentration in the mammary gland of a non-human farm mammal. It would take one skilled in the art an undue amount of experimentation to reasonably correlate raising the concentration of one immunoglobulin compared to another in any compartment of a mammal if the mammary gland is the only cells transfected with the nucleic acid construct. Thus, the claim is only enabled for: A method of making the transgenic farm mammal of 1, said method comprising: producing a DNA construct comprising a nucleic acid encoding pIgR protein operably linked to a promoter capable of driving expression of said pIgR protein in a mammary epithelial cell; introducing said DNA construct into fertilized eggs; and implanting the fertilized eggs into a pseudopregnant

female farm mammal, thereby product the transgenic farm mammal of 1), whereby the concentration of IgM or IgA is increased on the mammary gland cell's apical side compared to IgG on the mammary gland's basolateral side and not the full scope of the claimed method.

In addition, with respect to claims 1, 26, 32, 33, 34, which encompass using a mammary gland from a farm animal, the state of the art and the as-filed specification only provide sufficient guidance or evidence for one skilled in the art to make and/or use a transgenic farm mammal because the breadth of the claim encompasses any animal (chicken, duck, geese, etc.). One skilled in the art would interpret that the breadth of the claim encompasses any animal and there are many animals that do not produce milk or have mammary glands. Thus, in view of the reasons of record and the as-filed specification, it would take one skilled an undue amount of experimentation to reasonably extrapolate from making and/or using mammals that produce milk to making and/or using animals that do not produce milk. Therefore, the claimed invention is only enabled for making and/or using transgenic non-human farm mammals.

Furthermore, with respect to the breadth of the claimed embodiment encompassing a pIgR capable of transporting an immunoglobulin from an epithelial cell's basolateral side to the cell's apical side, the specification lack sufficient guidance for using any epithelial cell (*e.g.* liver, skin, etc.) other than a mucosal epithelial cell from a mammary gland in a transgenic non-human farm mammal. The specification is directed to transporting an immunoglobulin from an epithelial layer of mucosal or glandular surfaces (GI tract, respiratory tract, genital tract and mammary gland) into the external secretions. The specification does not reasonably correlate from generating transgenic mice over-expressing the murine pIgR in their mammary glands (epithelial cells) to any other tissue with epithelial cells (nasal, genital tract, liver, skin, etc.). For

example, human hepatocytes do not express pIgR (Lamm, Am. J. Physiol, Vol. 37, G614-G617, 1998). In view of the concerns discussed above, it would require an undue amount of experimentation for one skilled in the art to make and/or use a transgenic mammal comprising an epithelial cell over-expressing pIgR other than mucosal epithelial cell in a mammary gland. Thus, the claimed invention is only enabled for producing a transgenic mammal that over-expresses pIgR in mucosal epithelial cells in a mammary gland.

In addition, with respect to claim 31, the full breadth of the claim is not considered enabled because the working examples display that pIgR is exclusively found in a mammary gland when using a casein promoter. It is not apparent to one skilled in the art how to use the claimed method if the casein promoter is mammary gland specific and was used to express pIgR in any other epithelial cells. Thus, in view of the working examples displaying that pIgR is exclusively found in a mammary gland when using a casein promoter, the as-filed specification fails to provide sufficient guidance or evidence for how one skilled in the art would be enabled for using a casein promoter in any cell other than epithelial cells in a mammary gland.

In addition, with respect to claims 1 and 26, 29, 30, 31, 32, 33, 35, 36, which encompass transporting an immunoglobulin from the cell's basolateral side to the cell's apical side, the claims are not enabled for any immunoglobulin other than IgA and IgM because only IgM and IgA are able to pass through the epithelial layer and enter the secretion in a significant amount (Lamm, G614). Lamm teaches:

> Immunoglobulins that are not polymeric, such as IgG, the major class of antibody in serum, have no physiological means of reaching the external secretions. They do not

bind to the pIgR, and, like macromolecules generally, they are prevented from diffusing through the epithelium by the tight junctions that connect adjacent epithelial cells (G614). In view of the art of record and the lack of guidance provided by the as-filed specification for using any immunoglobulin other than IgA or IgM in the claimed invention, the specification is only enabled for transporting IgA or IgM from an epithelial cell's basolateral side to the cell's apical side.

Furthermore, with respect claim 32, the specification only teaches how to collect milk from a transgenic mammal that over-expresses pIgR in the mammary gland and does not teach how to collect milk from a transgenic farm mammal that does not over-express pIgR in its mammary gland. The breadth of the claim reads on using a transgenic animal with any epithelial cell over-expressing pIgR and the specification is only enabled for over-expressing pIgR in a mucosal epithelial cell in a mammary gland of a transgenic mammal.

Furthermore, with respect to claim 35, which is directed to administering a protein to enhance the expression of pIgR in a transgenic farm mammal, the specification cites that *in vitro* pIgR expression is enhanced when a protein selected from the group consisting of interferon-γ, interleukin-1, interleukin-4, and tumor necrosis factor-α. One skilled in the art would reasonably determine that the endogenous promoter was used in the *in vitro* experiments. The breath of the claim reads on using the proteins with any promoter (endogenous or exogenous) to enhance expression of pIgR in a transgenic farm mammal. However, the specification fails to provide sufficient guidance for one skilled in the art to use any exogenous promoter (e.g. LTR) in the claimed invention. Thus, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from enhancing the expression of pIgR operatively

linked to its endogenous promoter with the claimed proteins to using any promoter. Thus, in view of the lack of guidance provided by the specification the claim is not enabled.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only enable one skilled in the art to make and/or use 1-3 listed above. Given the lack of sufficient guidance or direction provided the specification for the providing a mammary gland of a non-human farm transgenic animal other then the transgenic mammals over-expressing a pIgR in its mammary gland compared to expression of pIgR in a mammary gland of a wild-type farm mammal, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 27, 32, and 36 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "immunoglobulin protein" in claim 27 is a relative term, which renders the claim indefinite. The term "immunoglobulin protein" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The disclosure does not define the metes and bound of the term. Claim 27 depends on claim 26, which recites, "transporting an immunoglobulin protein" and "comparison to another protein

located on the epithelial cell's basolateral side". Claim 27 does not define, which protein is being claimed.

The statement in claim 32, "... a transgenic farm animal from claim 26" is indefinite because it does not point out which transgenic animal **an** animal is referring to in the claim. The dependent claim should state "A method of collecting an immunoglobulin.... of **the** transgenic farm animal from claim 26".

Claim 36 recites the limitation "administering an antigen to said farm animal prior to collecting the milk from the mammary gland". There is insufficient antecedent basis for this limitation in the claim. Claim 36 depends on claim 31 and claim 31 does not recite collecting milk from the mammary gland.

The affidavit filed on 10/21/02 under 37 CFR 1.131 is sufficient to overcome the 102(a) rejection for claims 1 and 26-36 (deGroot et al., Transgenic Research, Vol. 8: 125-135, 1999).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal

Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
12/27/02

DAVE T. NGUYEN
PRIMARY EXAMINER